Please add the following new claims:

101. (New) The method of claim 38, wherein said putative modulator to be screened is a small molecule.

102. (New) The method of claim 101, wherein said small molecule inhibits TLR-4 mediation of the lipopolysaccharide mediated response.

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103, (New) The method of claim 101, wherein said small molecule inhibits the lipopolysaccharide mediated response.

II. RESPONSE TO OFFICE ACTION

A. State of the Claims

At the time of the Action, claims 38-40, 52-75 and 100 were pending. Claims 101-103 have been added. Claims 62 and 69 have been cancelled. Therefore claims 38-40, 52-61, 63-68, 70-75, and 101-103 are currently pending.

A marked version of the amendments to the claims is provided in Appendix A. A clean version of the pending claims as amended is provided for the Examiner's convenience in Appendix B.

B. The Claims are Definite Under 35 U.S.C. § 112, Second Paragraph

All of the pending claims are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully traverse this rejection. However, Applicants also respectfully note that they are unable to effectively address the rejection of claim 100 because no specific

grounds for its rejection have been provided under the second paragraph of 35 U.S.C. § 112. Applicants also note that the cover sheet of the Official Action does not list claim 100 as either allowed or rejected. Applicants respectfully request clarification as to the status of claim 100, and if rejected, the specific grounds for rejection.

i) The name TLR-4 is an art accepted term and definite in its meaning in light of the specification.

The Action rejects claims 38, 40, 52, 55, 56 and 62-64 and the claims that depend from them on the grounds that the name of TLR-4 has changed once in the literature, concluding that such changes render the use of the term TLR-4 indefinite. The Action further notes that proteins of a different name may exist that share the same structure and properties as that named as TLR-4. Applicants note that the rejection of claim 62 is moot in view of its cancellation. Applicants respectfully traverse the rejection as applied to the remaining claims.

A proper evaluation of the claims under the second paragraph of 35 U.S.C. § 112 requires that the claims be read in light of the specification. *North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1579, 28 USPQ2d 1333, 1339 (Fed. Cir. 1993). Furthermore, the law does not require that only immutable or invariant terms be used in claim language. Inventors are encouraged to use concise language with which they are familiar at the time of filing, as long as it is reasonably definite in view of the specification. This is long established law. *North Am. Vaccine, Inc.*, 7 F.3d 1571 at 1579; *Miles Lab., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993); *Loom Co. v. Higgins*, 105 U.S. (Otto.) 580, 586 (1881).

Claims may therefore make use of the language understood by those of skill in the art without additional, detailed definitions in the written description. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556-58, 220 USPQ 303, 315-16 (Fed. Cir. 1983). The name TLR-4 is in common use among artisans in the field in exactly the sense in which the Applicants

have defined it. See the attached Exhibit 1, which lists current references in the art using TLR-4 to refer to the instant polypeptides as the Applicants have defined them in the specification. The frequency of such use in the literature of the field of the invention demonstrates that the name TLR-4 has a well-known definition and is a well-known, even common, term in the art. Thus, a skilled artisan would understand the scope and content of the claims based upon the common understanding of the meaning of the name TLR-4.

Nevertheless, Applicants have provided a detailed and consistent definition of TLR-4 in the specification. Most particularly, TLR-4 as used by the Applicants refers explicitly to polypeptides of the sequences of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99 and those sequences at least about 85% similar thereto or biologically functional equivalents thereof. See the specification at page 30, lines 4-15 and page 73, line 18 through page 76, line 11. In view of the properties and structures of TLR-4 polypeptides thus supplied in the present specification Applicants respectfully submit that the specification sheds sufficient light upon the claims to render them clear and definite under the second paragraph of 35 U.S.C. § 112.

Therefore, viewed in light of the knowledge of one of skill in the art and the disclosure and definition provided in the specification, Applicants respectfully submit that claims 38-40, 52-68, 70-75 are not indefinite under the second paragraph of 35 U.S.C. § 112.

ii) Lipopolysaccharide mediated responses and the parameters used in their determination are provided in the specification.

Claims 38, 52, and 62 and the claims that depend from them are rejected on the grounds that they are indefinite because the term "lipopolysaccharide mediated response" and the parameters used to determine the response are not clear. The Action queries "where does the lipopolysaccharide pathway begin and end?"

Applicants note that the rejection of claim 62 is moot in view of its cancellation and respectfully traverse the rejection of the remaining claims.

Applicants refer to the specification at page 2, line 14 through page 4, line 24, and especially page 22 lines 3-7 for a succinct description of the events and circumstances that comprise the initiation of a response to LPS and the resultant responses.

Exemplary parameters and methods for measuring and determining the response are found in several locations in the specification: page 87, line 5 through page 88, line 15, Example 2 (page 95, line 25 through page 96, line 18), and Example 9 (page 123, line 1 through page 129, line 20). In the section of the Specification titled "Assays for LPS responsiveness" two examples of LPS-mediated response assays are described: a splenocyte proliferation assay and a macrophage response assay. See the specification at page 87, line 8 to page 88, line 15. The splenocyte response assay compares the proliferation of splenocytes incorporating tritiated thymidine (as measured by counts per minute, CPM) with and without stimulation with LPS. The macrophage response assay measures the per cent of cytotoxicity due to TNF released by cells in response to LPS. In yet another means of assaying for LPS response, TNF production may be directly measured. See the specification at page 3, lines 7-13, FIG. 15C, and page 87, line 23 through page 88, line 7. These are exemplary parameters and methods for measuring the LPS response. The specification thereby provides concrete examples, methods, and standards for measuring responses to LPS endotoxin mediated through TLR-4. Additional methods and parameters are available to the ordinary artisan through the knowledge of one of skill in the art.

Applicants respectfully submit that when viewed in light of these detailed descriptions of the responses to LPS endotoxin, how to measure them, and the role of TLR-4 in mediating those responses, the claims are definite under the second paragraph of 35 U.S.C. § 112.

iii) Claim 38 is definite as amended.

Claim 38 is additionally rejected on the grounds that the determination of the standard activity profile of TLR-4 renders the claim indefinite and that the claim is an unacceptable method claim.

Applicants have amended claim 38 to more clearly and particularly point out and describe their invention. As amended, claim 38 clearly denotes a valid method claim. Applicants respectfully request that the rejection on these grounds be withdrawn.

iv) Claim 52 is definite as amended.

The Action rejects claim 52 on the grounds that the "function of the modulator effected" is not clear and that the boundaries of the LPS mediated response are not clear. Applicants respectfully point out that the Action appears to have misinterpreted the claim language, substituting the putative modulator for TLR-4 in the syntax of the claim. Applicants have nevertheless amended claim 52 to claim the invention with more particularity and submit that the claim, as amended, is definite.

Further, the Action rejects claim 52 on the grounds that the boundaries of the LPS mediated response are indefinite. These grounds for rejection have been addressed above. Applicants respectfully submit that in view of the amendments and arguments presented claim 52 is definite under the second paragraph of 35 U.S.C. § 112.

v) The definition of a reporter gene is well known in the art and is therefore not indefinite.

Claim 40 is said to be indefinite because "it is not clear what is the reporter gene, what said gene reports and what is the promotor [sic] from a TLR-4 gene." Further, the Action alleges

that the Applicants do "not disclose where in the specification it is defined." Applicants respectfully traverse.

The specification utilizes the well known term of art "reporter gene" at page 10, lines 12-13, and page 127, lines 26-28 in contexts that make clear that the term is being used exactly as one of skill in the art would understand it. That is, a reporter gene is:

> "A coding sequence attached to heterologous promoter or enhancer elements and whose product is easily and quantifiably assayed when the construct is introduced into tissues or cells of the same origin as the regulatory elements. Reporter genes commonly used in the study of eukaryotic gene expression include bacterial genes encoding β-galactosidase (*lacZ*), chloramphenicol acetyltransferase (*cat*) and β-glucuronidase (*gus*)."

Encyclopedia of Molecular Biology, Kendrew (ed.), Blackwell Science Ltd., Oxford (1994), p. 953. One of ordinary skill in the art would thus understand that "what the reporter gene reports" is expression of the gene of interest, i.e. the product "easily and quantifiably assayed."

Applicants again respectfully point out that a proper evaluation of the claims under the second paragraph of 35 U.S.C. § 112 requires that the claims be read in light of the specification. *North Am. Vaccine, Inc.,* 7 F.3d 1571 at 1579. Applicants also note that the law does not require that the Applicants define in the specification every term of art well known to the artisan. Use of a well known term of art in the specification without detailed definitions thereof does not render claims utilizing that same language indefinite. *W.L. Gore & Assoc., Inc.* 721 F.2d 1540, 1556-58. If necessary, a standard reference work, such as the Encyclopedia of Molecular Biology (see above), may inform the reading of the specification, and if so, that in itself does not render claims utilizing that language indefinite. *Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 1382 (Fed. Cir. 1999) ("...even a dictionary or other documentary source may be resorted to...").

Given the ready availability of definitions of a reporter gene and knowledge of its use, the skilled artisan would readily understand what "reporter gene" means and how to use a reporter gene as invoked in the claims and provided in the specification. Therefore, the meaning of the term "reporter gene" in claim 40 is not indefinite under the second paragraph of 35 U.S.C. § 112.

Moreover, Applicants have provided a detailed definition and discussion of promoters in the specification. To wit: "A 'promoter' refers to a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a gene." See page 56, line14 through 18 and generally page 56, line 26 through page 59, line 2. A TLR-4 promoter is therefore a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate the specific transcription of a the gene encoding TLR-4. The terms thus defined in the specification render claim 40 definite under the second paragraph of 35 U.S.C. § 112.

Applicants respectfully request that the rejection of claim 40 on these grounds be withdrawn.

vi) The terms "small molecule inhibitor" are well known in the art and their meaning is not indefinite.

The meaning of the terms "small molecule inhibitor" is well established as referring to small molecules that inhibit whatever activity is involved in their application. In the interests of furthering the speedy prosecution of this case, however, Applicants have amended the claims so as to more particularly point out and distinctly claim the invention by more explicitly claiming small molecules that modulate or inhibit LPS mediated responses through their effects on TLR-4. See new claims 101-103. The rejection of claim 69 is moot in view of its cancellation.

vii) **The meaning of the terms "a stimulator of immune response" is provided in the specification and is also well known in the art and is therefore not indefinite.**

The Action rejects claim 71 under the second paragraph of 5 U.S.C. § 112 because the terms "stimulator of an immune response" are said to be lacking in structural limitations of the modulator and stimulated immune response. Applicants respectfully traverse.

Applicants again respectfully note that evaluation of the claims under the second paragraph of 35 U.S.C. § 112 requires that the claims be read in light of the specification and that Applicants need not define in the specification every term of art well known to the relevant artisan. *North Am. Vaccine, Inc.*, 7 F.3d 1571 at 1579; *W.L. Gore & Assoc., Inc.*, 721 F.2d 1540, 1556-58. Additionally, "under current law the specification of a patent consists of, and contains, both a written description of the invention and the claims." *In re Dossel*, 115 F.3d 942, 945 (Fed. Cir. 1997).

Stimulation of immune responses is a well known effect of the administration of compounds such as interferon and cytokines. Further, the structural definitions of cytokines and interferons and their stimulatory effects on the immune system are well known in the art. Indeed, the meaning of claim 71 is made clear at least in part by reference to claims 72 and 73, which depend from claim 71. Claim 72 recites the limitation "wherein said stimulator of an immune response is a cytokine." Claim 73 recites "wherein said stimulator of an immune response is an interferon." The structural limitations of a stimulator of an immune response are therefore typified by cytokines and interferons.

Applicants respectfully submit that claim 71, viewed in light of the specification, which includes the claims, is not indefinite under the second paragraph of 35 U.S.C. § 112.

viii) **Summary**

Applicants respectfully submit that claims 38, 40, 52, 55, 56, 62-64 and the claims depending upon them are not indefinite under 35 U.S.C. § 112, second paragraph. Applicants respectfully request withdrawal of the rejections.

C. The Pending Claims are Enabled.

The Action rejects claims 38-40, 52-75 and 100 under the first paragraph of 35 U.S.C. § 112. The Action alleges that the only screening method enabled is that which results in the altered expression of TLR-4 of SEQ ID NOS: 2, 4, 6, 98, or 99. Therefore, the Action concludes, methods of screening for modulators of LPS mediated responses through their interaction with TLR-4 are not enabled. Applicants respectfully traverse.

The pending claims are directed to methods of screening for modulators of a lipopolysaccharide mediated response that compare the response before and after contact of TLR-4 with a putative modulator or candidate substance. Altered expression of TLR-4 of SEQ ID NOS: 2, 4, 6, 98, or 99 may be one mode of LPS response that is measured, but it is by far not the sole means of modulating TLR-4 mediated LPS responses disclosed by the specification.

Applicants respectfully suggest that the Action mistakenly construed the fundamental nature of TLR-4 action and the invention. TLR-4 is a component of the signaling pathway that results in, for example, an increase TNF production as a result of lipopolysaccharide contact with cell surface receptors. Signaling in such a pathway is clearly described as involving multiple physical contacts among pathway components and other cellular constituents. See, for example, the specification at page 123, line 1 through page 129, line 20.

The sensitivity of the LPS mediated response may be directly effected by the endogenous levels of TLR-4 expression, but the LPS response itself may also be modulated by the nature of the physical interactions of TLR-4 with the other components of the pathway. Thus, altered isoforms of TLR-4, when co-expressed, interact with TLR-4 in modulating LPS mediated response. Another example of such effects includes the modulation of the intensity of the TLR-4 mediated response through interactions with interferon. See the specification at page 128, lines 20-26. Hence, modulation of LPS response through the modulation of TLR-4 activity, not merely its expression, is described and enabled by the specification.

In view of the disclosure provided in the specification and the clarification provided above, Applicants respectfully submit that the claims are enabled and that the rejection be withdrawn.

D. Conclusion

Applicants have submitted remarks which are believed to place the present claims in condition for allowance. In view of this, Applicants respectfully request that the present claims be passed for allowance. Should the Examiner have any comments or questions with regard to any statements contained herein, or any suggestions as to claim modification, the Examiner is respectfully requested to contact the Applicants' representative listed below.

Please date-stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,

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Date: November 14, 2001

APPENDIX A

CLAIMS PENDING IN USSN 09/396,985 AS MARKED FOR AMENDMENT.

38. (Twice Amended) A method of screening for modulators of a lipopolysaccharide mediated response comprising the steps of:

a) obtaining a TLR-4 polypeptide;

b) ~~determining a standard activity profile of~~measuring a lipopolysaccharide mediated response mediated by the TLR-4 polypeptide;

c) contacting the TLR-4 polypeptide with a putative modulator;

d) assaying for a change in the ~~standard activity profile;~~lipopolysaccharide mediated response; and

e) comparing the ~~standard activity profiles of~~lipopolysaccharide mediated responses mediated by the TLR-4 polypeptide obtained in steps b) and d) above

wherein a difference in the ~~standard activity profiles~~lipopolysaccharide mediated responses indicates that the putative modulator is a modulator of a lipopolysaccharide mediated response.

39. The method of claim 38, wherein the TLR-4 polypeptide has the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 or SEQ ID NO:99.

40. (Amended) The method of claim 39, wherein the ~~standard activity profile of~~lipopolysaccharide mediated response mediated by the TLR-4 polypeptide is determined by determining the ability of the TLR-4 polypeptide to stimulate transcription of a reporter gene, the reporter gene operatively positioned under control of a nucleic acid segment comprising a promoter from a TLR-4 gene.

52. (Twice Amended) The method of claim 38, wherein said putative modulator ~~affects the functioning of TLR-4 in~~is effective in altering the mediation of the lipopolysaccharide ~~pathway.~~mediated response by TLR-4.

53. The method of claim 52, wherein said putative modulator is an agonist.

54. The method of claim 52, wherein said putative modulator is an antagonist.

55. The method of claim 52, wherein said putative modulator affects the transcription of TLR-4.

56. The method of claim 52, wherein said putative modulator affects the translation of TLR-4.

57. The method of claim 38, wherein the TLR-4 polypeptide has the amino acid sequence of SEQ ID NO:2.

58. The method of claim 38, wherein the TLR-4 polypeptide has the amino acid sequence of SEQ ID NO:4.

59. The method of claim 38, wherein the TLR-4 polypeptide has the amino acid sequence of SEQ ID NO:6.

60. The method of claim 38, wherein the TLR-4 polypeptide has the amino acid sequence of SEQ ID NO:98.

61. The method of claim 38, wherein the TLR-4 polypeptide has the amino acid sequence of SEQ ID NO:99.

62. [Canceled]

63. The method of claim 38, wherein said putative modulator inhibits TLR-4 directed signaling of TNF secretion.

64. The method of claim 38, wherein said putative modulator stimulates TLR-4 directed signaling of TNF secretion.

65. The method of claim 38, wherein said putative modulator to be screened is obtained from a library of synthetic chemicals.

66. The method of claim 38, wherein said putative modulator to be screened is obtained from a natural source.

67. The method of claim 65, wherein said natural source is selected from the group consisting of animals, bacteria, fungi, plant sources and living marine samples.

68. The method of claim 38, wherein said putative modulator to be screened is a protein or peptide.

69. [Canceled]

70. The method of claim 38, wherein said putative modulator to be screened is a nucleic acid molecule.

71. The method of claim 38, wherein said putative modulator to be screened is a stimulator of an immune response.

72. The method of claim 71, wherein said stimulator of an immune response is a cytokine.

73. The method of claim 71, wherein said stimulator of an immune response is an interferon.

74. The method of claim 38, wherein said TLR-4 polypeptide is encoded by a nucleic acid sequence selected from the group comprising SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:46, SEQ ID NO:47 and SEQ ID NO:48.

75. The method of claim 38, wherein said putative modulator to be screened is an IL-1 receptor antagonist.

100. The method of claim 38, wherein the TLR-4 polypeptide has the amino acid sequence selected from the group comprising SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:98 and SEQ ID NO:99.

101. (New) The method of claim 38, wherein said putative modulator to be screened is a small molecule.

102. (New) The method of claim 101, wherein said small molecule inhibits TLR-4 mediation of the lipopolysaccharide mediated response.

103. (New) The method of claim 101, wherein said small molecule inhibits the lipopolysaccharide mediated response.